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(54) METHODS OF DIAGNOSIS OF BLADDER CANCER, COMPOSITIONS AND METHODS OF SCREENING FOR MODULATORS OF BLADDER CANCER

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(57) ABSTRACT

Described herein are genes whose expression are up-regulated or down-regulated in bladder cancer. Also described are such genes whose expression is further up-regulated or down-regulated in drug-resistant bladder cancer cells. Related methods and compositions that can be used for diagnosis, prognosis, or treatment of bladder cancer are disclosed. Also described herein are methods that can be used to identify modulators of bladder cancer.

METHODS OF DIAGNOSIS OF BLADDER CANCER, COMPOSITIONS AND METHODS OF SCREENING FOR MODULATORS OF BLADDER CANCER

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is related to U.S. S No. 60/302,814, filed Jul. 3, 2001; U.S. S No. 60/310,099, filed Aug. 3, 2001; U.S. S No. 60/343,705, filed Nov. 8, 2001; U.S. S No. 60/350,666, filed Nov. 13, 2001; and U.S. S No. 60/372,246, filed Apr. 12, 2001, each of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention relates to the identification of nucleic acid and protein expression profiles and nucleic acids, products, and antibodies thereto that are involved in bladder cancer; and to the use of such expression profiles and compositions in the diagnosis, prognosis, and therapy of bladder cancer. The invention further relates to methods for identifying and using agents and/or targets that inhibit bladder cancer.

BACKGROUND OF THE INVENTION

[0003] In the United States, over 50,000 new cases of bladder cancer are diagnosed annually, and more than 10,000 deaths will be attributed to bladder cancer. Bladder cancer is now the fourth most common cancer among American men and the ninth most common cancer among American women. It occurs three times more frequently in men than in women, and it occurs roughly twice more frequently in white versus black men.

[0004] Bladder cancer rarely occurs in people younger than 40 years of age, being primarily a disease of older men. Nonetheless, bladder cancer is a significant cause of illness and death in the United States. The risk of bladder cancer increases steeply with age, with over half of all bladder cancer deaths occurring after age 70. In white men older than 65, the annual disease rate of bladder cancer is approximately 2 cases per 1,000 persons; this contrasts with a rate of 0.1 cases per 1,000 persons younger than 65.

[0005] Within the United States, bladder cancer rates are higher among people who reside in northern versus southern states, and is higher for people who live in urban versus rural areas. Although this difference suggests that environmental as well as genetic factors may contribute to the development and progression of the disease, other studies confirm that certain genes play a role in bladder cancer. For example, expression of the tumor suppressor gene p53 has been associated with an adverse prognosis for patients with invasive bladder cancer. A retrospective study of 243 patients treated by radical cystectomy found that the presence of nuclear p53 was an independent predictor for recurrence among patients with mid to late stage tumors. Esrig, et al (1994) *N.E. J. Med.* 331:1259-64.

[0006] Urinary bladder cancers represent a spectrum of diseases that can be grouped into three general categories: superficial, invasive, and metastatic. The prognosis for treatment is highly dependent on the stage at which the tumor is first diagnosed. A unique aspect of bladder cancer treatment is that repeated surgical biopsy is an integral part of routine patient management. This has permitted the conduct of molecular genetic studies of tumors from specific stages of the disease. The results of these studies suggest that bladder cancers develop and progress along at least two discrete pathways, which may account for differences in invasiveness and metastatic potential. Incorporating molecular genetic factors into the current paradigm for diagnosis and treatment will optimize the probability of cure and allow the quality of life for bladder cancer patients to be maintained.

[0007] Early detection and treatment can prevent reoccurrence and progression of the disease to an incurable stage. Thus, the identification of novel diagnostic markers and therapeutic targets will improve the current treatment of bladder cancer patients. While industry and academia have identified novel sequences, there has not been an equal effort exerted to identify the function of these novel sequences in disease states. The elucidation of a role for novel proteins and compounds in disease states for identification of diagnostic markers and therapeutic targets is essential for improving the current treatment of bladder cancer patients. Accordingly, provided herein are methods that can be used in diagnosis and prognosis of bladder cancer. Additionally, provided herein are molecular targets for therapeutic intervention in bladder cancer and other related bladder diseases. Further provided are methods that can be used to screen candidate bioactive agents for the ability to modulate bladder cancer.

SUMMARY OF THE INVENTION

[0008] The present invention therefore provides nucleotide sequences of genes that are up- and down-regulated in bladder cancer cells. Such genes are useful for diagnostic purposes, and also as targets for screening for therapeutic compounds that modulate bladder cancer, such as hormones or antibodies. Other aspects of the invention will become apparent to the skilled artisan by the following description of the invention.

[0009] In one aspect, the present invention provides a method of detecting a bladder cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13.

[0010] In one embodiment, the present invention provides a method of determining the level of a bladder cancer associated transcript in a cell from a patient.

[0011] In one embodiment, the present invention provides a method of detecting a bladder cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13.

[0012] In one embodiment, the polynucleotide selectively hybridizes to a sequence at least 95% identical to a sequence as shown in Tables 1A-13.

[0013] In one embodiment, the biological sample is a tissue sample. In another embodiment, the biological sample comprises isolated nucleic acids, e.g., mRNA.

[0014] In one embodiment, the polynucleotide is labeled, e.g., with a fluorescent label.

[0015] In one embodiment, the polynucleotide is immobilized on a solid surface.

[0016] In one embodiment, the patient is undergoing a therapeutic regimen to treat bladder cancer. In another embodiment, the patient is suspected of having metastatic bladder cancer.

[0017] In one embodiment, the patient is a human.

[0018] In one embodiment, the bladder cancer associated transcript is mRNA.

[0019] In one embodiment, the method further comprises the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

[0020] In another aspect, the present invention provides a method of monitoring the efficacy of a therapeutic treatment of bladder cancer, the method comprising the steps of: (i) providing a biological sample from a patient undergoing the therapeutic treatment; and (ii) determining the level of a bladder cancer-associated transcript in the biological sample by contacting the biological sample with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13, thereby monitoring the efficacy of the therapy. In a further embodiment, the patient has metastatic bladder cancer. In a further embodiment, the patient has a drug resistant form of bladder cancer.

[0021] In one embodiment, the method further comprises the step of: (iii) comparing the level of the bladder cancer-associated transcript to a level of the bladder cancer-associated transcript in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

[0022] Additionally, provided herein is a method of evaluating the effect of a candidate bladder cancer drug comprising administering the drug to a patient and removing a cell sample from the patient. The expression profile of the cell is then determined. This method may further comprise comparing the expression profile to an expression profile of a healthy individual. In a preferred embodiment, said expression profile includes a gene of Tables 1A-13.

[0023] In one aspect, the present invention provides an isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Tables 1A-13.

[0024] In one embodiment, an expression vector or cell comprises the isolated nucleic acid.

[0025] In one aspect, the present invention provides an isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1A-13.

[0026] In another aspect, the present invention provides an antibody that specifically binds to an isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1A-13.

[0027] In one embodiment, the antibody is conjugated to an effector component, e.g., a fluorescent label, a radioisotope or a cytotoxic chemical.

[0028] In one embodiment, the antibody is an antibody fragment. In another embodiment, the antibody is humanized.

[0029] In one aspect, the present invention provides a method of detecting a bladder cancer cell in a biological sample from a patient, the method comprising contacting the biological sample with an antibody as described herein.

[0030] In another aspect, the present invention provides a method of detecting antibodies specific to bladder cancer in a patient, the method comprising contacting a biological sample from the patient with a polypeptide encoded by a nucleic acid comprising a sequence from Tables 1A-13.

[0031] In another aspect, the present invention provides a method for identifying a compound that modulates a bladder cancer-associated polypeptide, the method comprising the steps of: (i) contacting the compound with a bladder cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13; and (ii) determining the functional effect of the compound upon the polypeptide.

[0032] In one embodiment, the functional effect is a physical effect, an enzymatic effect, or a chemical effect.

[0033] In one embodiment, the polypeptide is expressed in a eukaryotic host cell or cell membrane. In another embodiment, the polypeptide is recombinant.

[0034] In one embodiment, the functional effect is determined by measuring ligand binding to the polypeptide.

[0035] In another aspect, the present invention provides a method of inhibiting proliferation of a bladder cancer-associated cell to treat bladder cancer in a patient, the method comprising the step of administering to the subject a therapeutically effective amount of a compound identified as described herein.

[0036] In one embodiment, the compound is an antibody.

[0037] In another aspect, the present invention provides a drug screening assay comprising the steps of: (i) administering a test compound to a mammal having bladder cancer or to a cell sample isolated therefrom; (ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell sample or mammal, wherein a test compound that modulates the level of expression of the polynucleotide is a candidate for the treatment of bladder cancer.

[0038] In one embodiment, the control is a mammal with bladder cancer or a cell sample therefrom that has not been treated with the test compound. In another embodiment, the control is a normal cell or mammal.

[0039] In one embodiment, the test compound is administered in varying amounts or concentrations. In another embodiment, the test compound is administered for varying time periods. In another embodiment, the comparison can occur after addition or removal of the drug candidate.

[0040] In one embodiment, the levels of a plurality of polynucleotides that selectively hybridize to a sequence at least 80% identical to a sequence as shown in Tables 1A-13 are individually compared to their respective levels in a control cell sample or mammal. In a preferred embodiment the plurality of polynucleotides is from three to ten.

[0041] In another aspect, the present invention provides a method for treating a mammal having bladder cancer comprising administering a compound identified by the assay described herein.

[0042] In another aspect, the present invention provides a pharmaceutical composition for treating a mammal having bladder cancer, the composition comprising a compound identified by the assay described herein and a physiologically acceptable excipient.

[0043] In one aspect, the present invention provides a method of screening drug candidates by providing a cell expressing a gene that is up- and down-regulated as in a bladder cancer. In one embodiment, a gene is selected from Tables 1A-13. The method further includes adding a drug candidate to the cell and determining the effect of the drug candidate on the expression of the expression profile gene.

[0044] In one embodiment, the method of screening drug candidates includes comparing the level of expression in the absence of the drug candidate to the level of expression in the presence of the drug candidate, wherein the concentration of the drug candidate can vary when present, and wherein the comparison can occur after addition or removal of the drug candidate. In a preferred embodiment, the cell expresses at least two expression profile genes. The profile genes may show an increase or decrease.

[0045] Also provided is a method of evaluating the effect of a candidate bladder cancer drug comprising administering the drug to a transgenic animal expressing or over-expressing the bladder cancer modulatory protein, or an animal lacking the bladder cancer modulatory protein, for example as a result of a gene knockout.

[0046] Moreover, provided herein is a biochip comprising one or more nucleic acid segments of Tables 1A-13, wherein the biochip comprises fewer than 1000 nucleic acid probes. Preferably, at least two nucleic acid segments are included. More preferably, at least three nucleic acid segments are included.

[0047] Furthermore, a method of diagnosing a disorder associated with bladder cancer is provided. The method comprises determining the expression of a gene of Tables 1A-13 in a first tissue type of a first individual, and comparing the distribution to the expression of the gene from a second normal tissue type from the first individual or a second unaffected individual. A difference in the expression indicates that the first individual has a disorder associated with bladder cancer.

[0048] In a further embodiment, the biochip also includes a polynucleotide sequence of a gene that is not up- and down-regulated in bladder cancer.

[0049] In one embodiment a method for screening for a bioactive agent capable of interfering with the binding of a bladder cancer modulating protein (bladder cancer modulatory protein) or a fragment thereof and an antibody which binds to said bladder cancer modulatory protein or fragment thereof. In a preferred embodiment, the method comprises combining a bladder cancer modulatory protein or fragment thereof, a candidate bioactive agent and an antibody which binds to said bladder cancer modulatory protein or fragment thereof. The method further includes determining the binding of said bladder cancer modulatory protein or fragment thereof and said antibody. Wherein there is a change in binding, an agent is identified as an interfering agent. The interfering agent can be an agonist or an antagonist. Preferably, the agent inhibits bladder cancer.

[0050] Also provided herein are methods of eliciting an immune response in an individual. In one embodiment a method provided herein comprises administering to an individual a composition comprising a bladder cancer modulating protein, or a fragment thereof. In another embodiment, the protein is encoded by a nucleic acid selected from those of Tables 1A-13.

[0051] Further provided herein are compositions capable of eliciting an immune response in an individual. In one embodiment, a composition provided herein comprises a bladder cancer modulating protein, preferably encoded by a nucleic acid of Tables 1A-13 or a fragment thereof, and a pharmaceutically acceptable carrier. In another embodiment, said composition comprises a nucleic acid comprising a sequence encoding a bladder cancer modulating protein, preferably selected from the nucleic acids of Tables 1A-13, and a pharmaceutically acceptable carrier.

[0052] Also provided are methods of neutralizing the effect of a bladder cancer protein, or a fragment thereof, comprising contacting an agent specific for said protein with said protein in an amount sufficient to effect neutralization. In another embodiment, the protein is encoded by a nucleic acid selected from those of Tables 1A-13.

[0053] In another aspect of the invention, a method of treating an individual for bladder cancer is provided. In one embodiment, the method comprises administering to said individual an inhibitor of a bladder cancer modulating protein. In another embodiment, the method comprises administering to a patient having bladder cancer an antibody to a bladder cancer modulating protein conjugated to a therapeutic moiety. Such a therapeutic moiety can be a cytotoxic agent or a radioisotope.

DETAILED DESCRIPTION OF THE INVENTION

[0054] In accordance with the objects outlined above, the present invention provides novel methods for diagnosis and prognosis evaluation for bladder disease (BD), e.g., cancer, including metastatic bladder cancer, as well as methods for screening for compositions which modulate bladder diseases. Also provided are methods and compositions for treating bladder disease. Various related conditions where these markers may be useful also, include, e.g., carcinoma in situ, various stages of papillary carcinomas; and such conditions in different stages, layers, structural portions, etc.

[0055] Recent advances in molecular medicine, generally, have increased the interest in tumor-specific cell surface antigens that could serve as diagnostic or prognostic markers, or as targets for various immunotherapeutic or small molecule strategies. Antigens suitable for immunotherapeutic strategies should be highly expressed in cancer tissues and ideally not expressed in other, e.g., normal, adult tissues. Expression in tissues that are dispensable for life, however, may be tolerated, as a physiological consequence of such expression would be limited. Examples of such antigens in cancers other than bladder cancer include Her2/neu and the B-cell antigen CD20. Humanized monclonal antibodies

TABLE 8A-continued

Genes predictive of bladder cancer progression

Pkey	ExAccn	UnigeneID	Unigene Title	R1	R2
438855	AW946276	Hs.6441	*Homo sapiens* mRNA; cDNA DKFZp586J021 (fr	2.24	1.77
448718	AA220235	Hs.153959	hypothetical protein MGC15436	1.52	2.65
402685			Target Exon	2.04	2.46
424528	AW073971	Hs.238954	ESTs, Weakly similar to KIAA1204 protein	1.66	2.05
422068	AI807519	Hs.104520	*Homo sapiens* cDNA FLJ13694 fis, clone PL	1.89	4.98
451225	AI433694	Hs.293608	ESTs	1.79	2.70
441078	AI453268	Hs.323409	*Homo sapiens* cDNA FLJ14113 fis, clone MA	1.44	2.58
409406	H83092	Hs.49605	ESTs	1.38	2.05
422297	AW961290		p30 DBC protein	1.20	2.73
408711	AW376061	Hs.63335	ESTs, Moderately similar to A46010 X-lin	1.20	2.08
426696	AW363332	Hs.171844	*Homo sapiens* cDNA: FLJ22296 fis, clone H	1.35	2.68
417324	AW265494		ESTs	1.68	1.25
408283	BE141579		gb: QV2-HT0083-071299-018-b05 HT0083 Homo	1.25	2.65
415166	NM_003652	Hs.78068	carboxypeptidase Z	1.34	1.09
406300			Target Exon	1.61	2.47
411880	AW872477		gb: hm30f03.x1 NCI_CGAP_Thy4 *Homo sapiens*	3.60	4.03
422287	F16365	Hs.114346	cytochrome c oxidase subunit VIIa polype	2.16	1.44
422567	AF111178	Hs.118407	glypican 6	1.57	2.03
436855	AA732624	Hs.165852	ESTs	1.08	2.75
403536			Target Exon	0.93	2.13
447733	AF157482	Hs.19400	MAD2 (mitotic arrest deficient, yeast, h	1.18	1.07
417117	N46778		gb: yy52b02.r1 Soares_multiple_sclerosis_	1.70	2.85
411690	AA669253	Hs.136075	RNA, U2 small nuclear	2.12	2.78
443243	AI452496	Hs.132056	ESTs	1.15	2.83
423074	AL109963		FSH primary response (LRPR1, rat) homolo	1.37	1.43
408916	AW295232	Hs.429	ATP synthase, H transporting, mitochondr	1.63	2.23
449799	AI143466	Hs.125060	ESTs	1.40	2.08
415378	T16964		gb: NIB2079-5R Normalized infant brain, B	1.88	1.85
431089	BE041395		ESTs, Weakly similar to unknown protein	1.57	2.57
434959	AW974949	Hs.186564	ESTs, Weakly similar to I38022 hypotheti	1.30	2.30
416311	D80529		gb: HUM081H05B Human fetal brain (TFujiwa	1.58	4.35
444614	R44284	Hs.2730	heterogeneous nuclear ribonucleoprotein	1.88	2.98
456206	NM_006895	Hs.81182	histamine N-methyltransferase	1.24	2.08
410583	AW770280	Hs.36258	ESTs, Moderately similar to JC5238 galac	1.56	4.33
430410	AF099144	Hs.334455	tryptase beta 1	1.91	1.58
408139	AA451966		RAB9-like protein	1.42	2.14
432621	AI298501	Hs.12807	ESTs, Weakly similar to T46428 hypotheti	2.08	1.94
441584	AW148329	Hs.175208	ESTs	1.12	2.05
445940	D60438	Hs.34779	ESTs	1.86	2.70
453022	AA031499	Hs.118489	ESTs	2.02	1.75
444008	BE544855	Hs.236572	ESTs, Weakly similar to SFR4_HUMAN SPLIC	1.54	1.29
442994	AI026718	Hs.16954	ESTs	3.60	3.78
402085			C18000504*: gi|2627436|gb|AAB86683.1| (AF	1.36	2.53
411918	AW876354		gb: PM4-PT0019-141299-009-F08 PT0019 Homo	2.00	2.63
455508	AW976165		gb: EST388274 MAGE resequences, MAGN Homo	1.70	3.04
426106	AI678765	Hs.21812	ESTs	1.49	2.11
425131	BE252230	Hs.99163	ESTs	2.04	2.65
440325	NM_003812	Hs.7164	a disintegrin and metalloproteinase doma	1.17	2.55
420447	AA687306	Hs.88448	ESTs	1.66	2.58
428055	AA420564	Hs.101760	ESTs	1.08	2.15
422110	AI376736	Hs.111779	secreted protein, acidic, cysteine-rich	1.76	1.82
438581	AW977766	Hs.292133	ESTs, Moderately similar to I78885 serin	1.08	2.10
403290			C1000101*: gi|4758212|ref|NP_004411.1| d	0.97	2.48
408175	W29089	Hs.19066	hypothetical protein DKFZp667O2416	1.42	1.41
432390	AA936177	Hs.274460	olfactory receptor, family 5, subfamily	1.26	2.05
443441	AW291196	Hs.92195	ESTs	1.52	2.13
419925	AA159850	Hs.93765	lipoma HMGIC fusion partner	1.72	2.80
445256	AI858635	Hs.144763	ESTs	1.97	3.33
456381	AA236606		gb: zr99b10.r1 NCI_CGAP_GCB1 *Homo sapiens*	1.16	1.95
422433	AA310560	Hs.153746	hypothetical protein FLJ22490	1.06	2.20
432529	AI989507	Hs.162245	ESTs	1.36	2.25
424951	AW964082		gb: EST376155 MAGE resequences, MAGH Homo	2.22	2.58
420785	H89633	Hs.191346	ESTs	1.26	2.15
411347	AW838126		gb: QV2-LT0051-240300-097-f01 LT0051 Homo	1.38	2.38
438742	AW204126	Hs.196543	ESTs	1.10	2.30
414900	AW452420	Hs.248678	ESTs	2.01	3.08
443284	AI369813	Hs.64783	ESTs, Weakly similar to T42705 hypotheti	0.66	0.43
402049			Target Exon	2.28	2.00
429400	AW604940	Hs.201668	transcription factor 20 (AR1)	1.16	2.00
423916	AW993496	Hs.17235	*Homo sapiens* clone TCCCIA00176 mRNA sequ	1.59	1.05
432495	AW973537	Hs.186734	ESTs, Weakly similar to I61746 pheromone	1.50	2.05
414840	R27319	Hs.23823	hairy/enhancer-of-split related with YRP	1.89	2.09

What is claimed is:

1. A method of detecting a bladder cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13.

2. The method of claim 1, wherein the biological sample comprises isolated nucleic acids.

3. The method of claim 2:

a) wherein the nucleic acids are mRNA; or

b) further comprising the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

4. The method of claim 1, wherein the polynucleotide:

a) comprises a sequence as shown in Tables 1A-13; or

b) is immobilized on a solid surface.

5. The method of claim 1, wherein the patient is:

a) undergoing a therapeutic regimen to treat bladder cancer; or

b) suspected of having bladder cancer.

6. An isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Tables 1A-13.

7. The nucleic acid molecule of claim 6, which is labeled.

8. An expression vector comprising the nucleic acid of claim 7.

9. A host cell comprising the expression vector of claim 8.

10. An isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Tables 1A-13.

11. An antibody that specifically binds a polypeptide of claim 10.

12. The antibody of claim 11, further conjugated to an effector component.

13. The antibody of claim 12, wherein the effector component is a fluorescent label.

14. The antibody of claim 12, wherein the effector component is a radioisotope or a cytotoxic chemical.

15. The antibody of claim 11, which is

a) an antibody fragment; or

b) a humanized antibody

16. A method of detecting a bladder cancer cell in a biological sample from a patient, the method comprising contacting the biological sample with an antibody of claim 11.

17. The method of claim 16, wherein the antibody is further conjugated to an effector component.

18. The method of claim 17, wherein the effector component is a fluorescent label.

19. A method for identifying a compound that modulates a bladder cancer-associated polypeptide, the method comprising the steps of:

a) contacting the compound with a bladder cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13; and

b) determining the functional effect of the compound upon the polypeptide.

20. A drug screening assay comprising the steps of

a) administering a test compound to a mammal having bladder cancer or a cell isolated therefrom;

b) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1A-13 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that modulates the level of expression of the polynucleotide is a candidate for the treatment of bladder cancer.

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